Does the circadian pattern for acute cardiac events presentation vary with fasting?

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ABSTRACT

Background: Over one billion Muslims fast worldwide during the month of Ramadan. The impact of fasting on circadian presentation with acute cardiac events is unknown.

Aim: To determine if fasting has any effect on the circadian presentation of acute cardiac events.

Setting and Design: A prospective study in a general hospital.

Materials and Methods: Patients with acute coronary events were divided into two groups based on the history of fasting. Information about age, gender, cardiovascular risk factor profiles, and outcome was collected. The relationship of time of presentation of initial symptoms with fasting was evaluated using Student's t-test, Mann-Whitney U-test, and χ^2 analysis.

Results: Of the 1019 patients hospitalized during the study period, 162 were fasting. Although, fasting patients were more likely to present to the emergency department in the time periods 5–6 AM (10.5% *vs* 6.3%) and 11 PM (11.1% *vs* 7.1%) and were less likely to present in the time periods 1–2 PM (3.7% *vs* 7.2%) and 5–6 PM (3.7% *vs* 7.0%); these differences were not statistically significant. Fasting patients were less likely to have their symptoms start between 5 and 8 AM (11.1% *vs* 19.4%) and more likely to have symptoms between 5 and 6 PM (11.1% *vs* 6.0%) and 3 and 4 AM (11.1% *vs* 6.9%). These differences for time of initial symptoms were statistically significant (P=0.002).

Conclusion: Exogenous factors associated with fasting, namely, the changes in food intake and/or sleep timings, affect the circadian rhythm and influence the timing of presentation of acute coronary events.

KEY WORDS: Acute coronary syndrome, Ramadan fasting, coronary heart disease

One of the five fundamental rituals of Islam, the religion professed by over one billion people worldwide, is fasting during the month of Ramadan. The time of observance differs each year because the timing of Ramadan is decided by the lunar calendar. The devotees are supposed to fast from dawn to sunset and the duration of fasting every day depends on the geographical site and season. For example, in the summer months, the fast could last up to 18 h or more in northern latitudes. Muslims observing the fast must not only abstain from eating and drinking, but also from taking oral medications as well as intravenous fluids and nutrients. Fasting is not obligatory for children, menstruating women, sick individuals, and travelers.[1–3]

During the months of the Ramadan fast, devotees take two meals, one before sunrise and the other shortly after sunset. This change of meal schedule is accompanied with changes in the sleep habit (shortening of time to sleep).[1] It was thought that a change in the number and timing of meals, portioning the entire intake into two (instead of the usual four or five), and alterations in the schedule of drug intake could have an effect on patients with cardiac diseases.[3] Several investigators have shown lack of significant differences in the number of hospitalizations for acute coronary syndromes and congestive heart failure (CHF) during periods of fasting.[3–5] However, this study has been undertaken to evaluate the effect of fasting on the circadian pattern of cardiac events that have not been elaborated upon to date.

Materials and Methods

Study setting

This prospective study, based at a general hospital in this country, was carried out over a period of nine months beginning October 2002, after obtaining clearance from the institutional ethics committee.[3] This hospital provides inpatient and outpatient medical and surgical care for the resident nationals and expatriates. All patients with acute heart disease events requiring hospitalization in the country are treated at this hospital. Access to health care in Ramadan is comparable with

that for the rest of the year. In addition to demographic information and data regarding cardiovascular risk factors (smoking status, hypertension, hypercholesterolemia, diabetes, and pre-existing coronary heart disease), data regarding fasting, time of beginning of symptoms, final diagnosis, therapy given, and outcome were recorded.

Ramadan and time periods

Periods corresponding to the month of Ramadan in the Gregorian calendar have been established, because the lunar calendar is 11.12 days shorter than the solar year. In 2002, the month of Ramadan started on 5th November and ended on 4th December. The daily time periods were divided into twelve time periods beginning from 5 AM (meal time before sunrise). The usual fasting time extended from 5 AM to 4 PM, when no food or drink was consumed and fasting people remained asleep for a longer time. Muslims break their fast between 4 PM and 7 PM and the largest meal is taken during this period. Between 7 PM and 3 AM, they are allowed to eat and drink. Therefore,, sleeping patterns are changed and they remain awake during these hours.

Definitions

CHF was defined using the Framingham Heart Study criteria and acute coronary syndromes including acute myocardial infarction (AMI) and unstable angina were defined according to the World Health Organisation[3]/World Health Organization's norms/criteria. Use of adjunct therapy during hospitalization was recorded for every patient. The presence of diabetes mellitus was determined by the documentation in the patient's current medical record of a documented diagnosis of diabetes mellitus that had been treated with medication or insulin. The presence of hyperlipidemia was determined by the demonstration of a fasting cholesterol > 5.2 mM/l in the patient's medical record, or any history of treatment for hyperlipidemia by the patient's physician.

The presence of hypertension was determined by any documentation in the medical record or if the patient was on treatment for hypertension.

Smoking history

Patients were divided into current cigarette smokers and past smokers—the latter defined as more than 6 months' abstinence from smoking, and those who never smoked.[3]

Statistical analysis

The data were coded and entered into a computer using the Statistical Packages for Social Sciences (SPSS), Norusis.[6] Data are expressed as mean ± standard deviation (SD) unless otherwise stated. Student's *t*-test was used to ascertain the significance of differences between mean values of two continuous variables and Mann-Whitney test was used for nonparametric test. χ^2-analysis was performed to test for differences in proportions of categorical variables between the two groups. Uniformity was evaluated by a 2-h interval using a χ^2-test for goodness-of-fit test as a nonparametric statistical test. All analyses were done at 5% significance.

Results

One thousand and nineteen patients admitted to the coronary care unit and cardiology wards during the study period were included. Of these, 162 patients were fasting on the day of presentation. The baseline clinical characteristics of the subjects in the two groups (fasting and nonfasting) are shown in Table 1. There was no significant difference between the two groups in terms of age. The mean age of fasting subjects was 57.6±12.9 years, whereas that for nonfasting subjects was 56.6±13.6 years, the proportion of subjects with unstable angina and congestive cardiac failure were compared. However, the proportion of subjects presenting with AMI was significantly higher in the fasting group (79.6% *vs* 47.0; $P<0.001$). As shown in Table 2, there was no significant difference between the two groups as far as the therapeutic modalities employed at presentation were concerned.

Figures 1 and 2 depict the circadian variation in the time of symptom-onset and emergency room presentation in relation to fasting. There were significant differences ($P=0.002$) between the two groups with respect to time of beginning of symptoms. Fasting patients were less likely to have their symptoms start between 5 AM and 8 AM (11.1% *vs* 19.4%) and were more likely to have symptoms between 5 PM and 6 PM (11.1% *vs* 6.0%) and between 3 AM and 4 AM (11.1% *vs* 6.9%), corresponding to the timing of meal schedule for fasting patients. The fasting patients were also more likely to present to the emergency department in the time periods 5 AM to 6 AM (19.1% *vs* 15.8%) and from 11 PM to midnight (11.1% *vs* 7.1%). The fasting patients were less likely to present to the emergency

Table 1: Characteristics of patients with acute coronary heart disease events according to the fasting status

Characteristics	Fasting (*n*=162)	Not fasting (*n*=857)	Relative risk (95% CI)	*P*
Gender				
Male	118 (72.8)	642 (74.9)	0.9 (0.7–1.3)	0.578
Female	44 (27.2)	215 (25.1)		
Diagnosis				
Myocardial infarction	129 (79.6)	403 (47.0)	3.6 (2.5–5.1)	<0.001
Unstable angina	61 (37.7)	262 (30.6)	1.3 (1–1.7)	0.076
CHF	31 (19.1)	168 (19.6)	1 (0.6–1.5)	0.891

Figures in parentheses indicate percentages.

Table 2: Therapeutic measures required at the time of admission

Admission therapy	Fasting (*n*=162)	Not fasting (*n*=857)	Relative risk (95% CI)	*P*
B-blockers	94 (58.0)	487 (56.8)	1.0 (0.7–1.5)	0.777
ACE inhibitors	72 (44.4)	395 (46.1)	0.9 (0.7–1.3)	0.7
Aspirin	145 (89.5)	734 (85.6)	1.4 (0.9–2.2)	0.191
Calcium-channel blockers	13 (8.0)	57 (6.7)	1.2 (0.7-2.0)	0.874
Digoxin	13 (8.0)	72 (8.4)	1.0 (0.6-1.6)	0.526

Figures in parentheses indicate percentages.

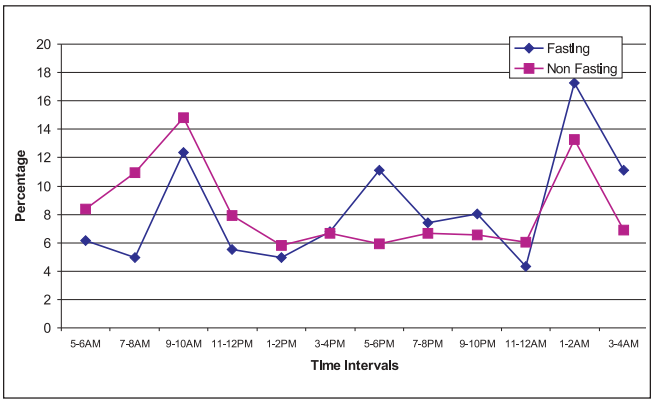

Figure 1: χ^2 Goodness-of-fit test (P= 0.002); degree of freedom=1

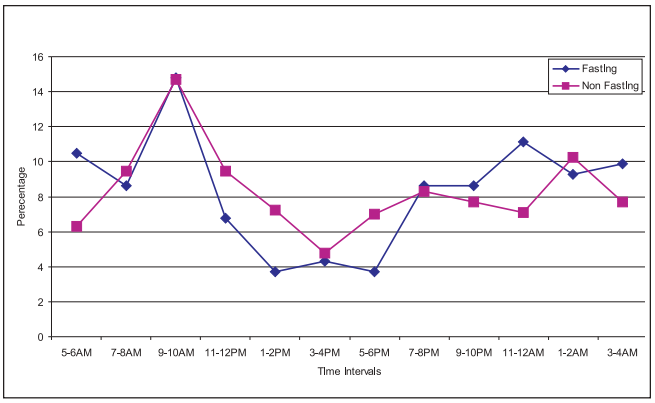

Figure 2: χ^2 Goodness-of-fit test (P = 0.62); degree of freedom=1

department between 1 PM and 2 PM (3.7% *vs* 7.2%) and between 5 PM and 6 PM (3.7% *vs* 7.0%). However, these differences were not statistically significant.

Discussion

In healthy humans, heart rate and blood pressure increase during the day and decrease during the night. In addition, other cardiovascular parameters, such as vascular tone, cardiac output, and haemostatic-fibrinolytic indices have circadian rhythms. Influences of both external stimuli and endogenous mechanisms, including autonomic activity and release of catecholamines, cortisol, and melatonin are responsible for these diurnal variations.[7–9] On the days of fasting, the "normal" circadian pattern changes among the fasting Muslims. In addition to changes in the meal schedule, sleep pattern also changes, as fasting subjects remain awake during the night and spend most of the daytime sleeping.[3,4] It is possible that these changes could exert an exogenous effect on the circadian rhythm. We took up this unique opportunity to examine if changes in eating and sleeping pattern have an influence on the circadian pattern of acute cardiac events.

Interestingly, it has been known since the late 1980s that almost all cardiovascular events exhibit a pronounced circadian rhythm with acute coronary syndromes, stroke, malignant arrhythmias, sudden cardiac death, and heart failure being more common in the morning when patients wake up, resume an upright posture, and begin activities than during sleep.[5,8,10–16] This timing is consistent with the timing of a surge in a series of physiological parameters: heart rate, blood pressure, blood concentration of epinephrine and norepinephrine, angiotensin II level, cortisol secretion, and platelet aggregability.[8,13,15] During this time, myocardial oxygen demand increases, whereas its supply may decrease (because of an increase in coronary vascular tone). In addition, coagulation activity is increased and fibrinolytic activity is decreased. Exogenous influences may have a role, as was reported with stressful events and postural changes. Together, these phenomena can account for the increased risk of ischemic events in the morning hours.

The current study is consistent with previous studies in finding a circadian pattern in acute cardiac events' presentations. Furthermore, it suggests that exogenous factors associated with fasting (changes in food intake and sleep pattern) may play an important role in the circadian pattern of cardiovascular diseases. This observation is supported by previous studies that documented an association between fasting in Ramadan with hematological, biochemical, hormonal, and mood and alertness changes that may influence the circadian pattern of acute cardiac events.[17–22] A number of studies revealed alterations in the circadian secretions in plasma gastrin, insulin, cortisone, and testosterone secretions. Some of these changes have been shown to influence the circadian pattern of cardiac events such as cortisol. Aybak *et al.*[17] documented a significant increase in bleeding and coagulation time and a decrease in the platelet responses to different aggregation agents (adenosine diaphosphate, adrenaline, and collagen) by the end of Ramadan in 20 healthy, nonsmoking male volunteers. Their study was, however, limited by the fact that circadian evaluation in relation to fasting was not performed.

Other studies that support our observation[23–26] include a study that documented reduction of cardiac events during hunger. Hunger has been associated with catecholamine inhibition (catecholamine surge has been implicated as a trigger for acute coronary syndromes) and reduced venous return, causing a decrease in the sympathetic tone, which leads to a fall in blood pressure, heart rate and cardiac output.[23] In a recent study, Hussein *et al.*[24] reported a reduction in heart rate during Ramadan, concluding that this was owing to the inhibition of catecholamine production during hunger. Similar findings were observed in 18 healthy volunteers undergoing moderately heavy aerobic exercise tests during and 1 month after Ramadan.[25] Moreover, a recent study suggested that nutrition might have a role in circadian rhythm and subsequently, cardiac events; for example, plasma levels of vitamin E and C were shown to exhibit a circadian pattern and hence nutrition timing changes may have a role.[26] Hence it is not surprising to observe these changes in circadian pattern have an effect on the presentation acute cardiac events during fasting.

However, in a retrospective analysis of all national patients hospitalised in this country between 1991 and 2001, there were

no significant differences found in the incidence of acute coronary syndromes or CHF among Ramadan when compared to the rest of the year (in a population in which more than 90% of the endogenous population regularly fast in Ramadan).[3,4] Other investigators reported similar findings.

Conclusion

This study demonstrates that there are significant changes in the circadian presentation of patients with acute heart events in relation to fasting, emphasising the importance of the exogenous factors that are associated with fasting; namely, the changes in food intake and/or sleep timing, and their effects on the circadian rhythm of acute heart events.

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Expert's Comments

Does ramadan modify the circadian patterns?

During the month of Ramadan, adult Muslims abstain from drinking and eating daily between sunrise and sunset. Because this is Muslim lunar calendar, the timing of this month of fast changes each year and the duration of restricted food and beverage intake can vary from between 12 and 16 h. This change of meal schedule is accompanied with changes in sleep habits, such as delayed and shortened sleep periods, which may affect endocrine and neuroendocrine circadian patterns. Several cardiovascular parameters (i.e., heart rate, blood pressure, vascular tone, and coagulation-fibrinolysis) show circadian pattern. Several studies reported that autonomic activity and melatonin rhtyhmicity may be responsible for circadian patterns of cardiovascular parameters.[1–3] Changes of sleep habit in Ramadan affects autonomic activity and melatonin rhtyhmicity. The other negative effects may be that, during fasting patients with cardiovascular disease cannot consume medications, such as anti-ischemic, anti-platelet, anti-hypertensive drugs, and drugs of heart failure on time. Some patients may get admitted to the hospital with cardiovascular symptoms owing to failure of therapy.

However, some studies reported that Ramadan fasting does not increase acute coronary syndrome. The present study revealed increased acute myocardial infarction rate in fasting subjects. In addition, it first showed circadian presentation of these patients. This important finding supports Ramadan fast-

ing, namely, changes of food intake and sleep habit, affects the circadian cardiovascular patterns owing to changes in autonomic activity and melatonin rhtyhmicity.

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